clinical involvement of other muscles supplied by the C7 or C8 segments.

Lesions of the spinal anterior horns in syringomyelia usually cause amyotrophy that begins in the small muscles of the hands, ascends to the forearms, and ultimately affects muscles of the shoulder girdle. The clinical presentation of our patient with isolated paresis of the serratus anterior and triceps muscles is therefore very unusual.

Apart from the intramedullary syrinx at C7/T1, cervical MRI also demonstrated a small hindbrain hernia. Syringomyelia usually arises as a result of an associated anomaly,—for example, the Arnold-Chiari malformation; the demonstrated hernia thus may be the aetiology of the syrinx.

Another interesting finding in this patient is the combination of syringomyelia with movement disturbances. Dystonia and other movement disorders in syringomyelia are rare, but have been recorded.[5 6] Nevertheless, careful clinical examination suggested psychogenic dystonia in this patient.

The present case illustrates that a central lesion presumably of the C7 and C8 spinal cord segments may damage the serratus anterior motor nucleus on both sides and thus may cause bilateral scapular winging thereby mimicking a neuromuscular disorder.

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Focal neuropathy associated with cutaneous necrosis at the site of interferon-β injection for multiple sclerosis

Interferon-β is the first approved treatment for relapsing multiple sclerosis. Although generally well tolerated, it is sometimes associated with cutaneous reactions at the injection site. To decrease local side effects, it has been suggested that injection sites in the belly, the thigh, and the arms are regularly changed. These cutaneous reactions range from slight erythema to necrosis. We report the first mononeuropathy associated with local adverse reaction after interferon-β injection.

A 39 year old woman had a 15 year history of multiple sclerosis, and a 3 year history of secondary progressive phase (EDSS=6). She had been treated for 3 years with subcutaneous interferon-β 1b (Betaferon®) every other day, when a painful violaceous, livedoid pattern on the skin of the posterior aspect of the right upper arm appeared, at a site of injection at the mid-portion of the humerus. Two days later, a necrotic ulcer (diameter 10 mm, depth 2 mm) occurred. Concomitantly, she experienced tingling on the dorsal aspect of the thumb without motor or reflex abnormalities. The livedo lasted a month, and the spontaneous ulcer healed in the same time. The sensory dysfunction recovered 10 months after onset. The following laboratory tests were negative or normal: glycaemic tests, antinuclear antibodies, rheumatoid factor, complement fractions, cryoglobulin, thyroid tests, and anticardiolipin antibodies.

Radial neuropathy was confirmed by neurophysiological testing performed 3 months after the onset. A motor conduction block (80% reduction of the compound muscle action potential amplitude) was found on the right radial nerve at the level of the injection site related necrosis. In addition, cutaneous thermal thresholds (TSA-2001, Medoc, Ramat, Israel) in the right radial nerve territory were significantly higher than the contralateral ones, whereas radial sensory nerve action potential amplitudes were normal and symmetric (right 82 μV; left 92 μV). Ten months after onset, the conduction block had disappeared and thermal thresholds were normal.

Cutaneous necrosis occurred in 1% to 3% of patients treated by interferon-β1b.[1] Necrosis may be favoured by an inadequate injection technique, not rotating the injection sites, or absence of heating of the diluent before the injection. Cutaneous necrosis associated with interferon-β injection is thought to potentially combine inflammatory and ischaemic local damage.[2] The pathophysiological mechanism of the focal neuropathies can only be hypothetical, but several features of our case suggest an ichaemic mechanism. Conduction block in motor nerve fibres is a feature of ischaemic nerve injury.[3] The discrepancy between thermal sensory impairment and normal sensory nerve action potential amplitude is consistent with the higher susceptibility to ischaemia of smaller nerve fibres[4]; Raynaud's phenomenon has been recently reported as the first evidence of ischaemic lesion induced by interferon-β injection for multiple sclerosis.[5]

This led us to avoid some recommended sites of injection, which correspond to the anatomical course of peripheral nerves. These include the posterior aspect of the arm to preserve the radial nerve, the lateral abdominal wall, and close to the anterior superior iliac spine, to preserve the lateral femoral cutaneous nerve, and the upper aspect of the buttock to preserve the sciatic nerve.

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Treatment with intravenous prednisone and immunoglobulin in a case of progressive encephalomyelitis with rigidity

The progressive encephalomyelitis with rigidity syndrome (PEMRS) is a rare neurological disorder that can be considered as the most severe form of the "stiff person" syndrome[1 2] although other authors suggest that it may be a distinct entity.[3] Pathogenesis is far from being clearly defined, but some studies point to humoral immunity as having an important role. Antiglutamic acid decarboxylase (anti-GAD) antibodies have been found to be present in about 40% of patients with stiff person syndrome.[4] Treatment is very difficult and in the only case reported so far in which intravenous immunoglobulin has been used the response was poor.[2] We report a case of PEMRS with anti-GAD antibodies that had an excellent response to intravenous immunoglobulin.

A 67 year old woman was admitted to our hospital with a 9 month history of progressive gait disturbance and painful leg contractions. Family history was negative for neurological disorders. General examination was unremarkable. On neurological examination she showed marked stiffness in her legs and painful spasms; these appeared spontaneously but could also be elicited by external events such as touch, noise, and frightening. The examination was otherwise normal.

Brain and spinal MRI did not show any abnormality. Both needle EMG and nerve conduction were normal except for spontaneous firing of motor units. Blood tests including vitamin B_{12} and folic acid, C_3, C_4, thyroid hormones, antithyroglobulin antibodies, syphilis serology, and CSF examination were all within normal limits. Anti-GAD autoantibodies were positive, both in serum (1/16000 IU with histochemistry and 1/30325 IU/ml with radioimmunoassay (RIA) and in the CSF (1/40 IU with histochemistry).

For unknown reasons, a week after admission the clinical course changed: the patient seemed to be confused, became disoriented, and her consciousness was clearly impaired. The spasms were more severe and neurological examination showed bilateral pyramidalism with Babinski's sign. The clinical picture corresponded to a progressive encephalopathy, This was confirmed by EEG (generalised slow waves). We started treatment with valproate, gabapentin, and diazepam but lack of improvement led us to try intravenous immunoglobulin (0.4 g/kg/24 hours for 5 days and then the same dosage every 2 days) together with intravenous methylprednisolone (80 mg/24 hours). A positive response appeared at the 5th day. After 7 days of treatment she regained normal consciousness and did not show any spasms.

However, 6 weeks later the patient presented with gait disturbances again. Anti-GAD autoantibodies were again positive in serum (1/8000 IU with histochemistry and

1/36250 IU/ml with RIA) and in the CSF (1/20 IU with histochemistry). For this reason, immunoglobulin (0.4 g/24 hours for 5 days) was used again with prednisone (60 mg/24 hours orally (the previous dose had been reduced to 40 mg/48 hours)). Six months after admission she continued free of spasms, with a total independence for daily life activities, but on examination she had a mild loss of memory and a mild loss of strength in both hands.

The aetiology of both stiff person syndrome and PEMRS remains unknown although an autoimmune mechanism has been suggested. Therefore, plasmapheresis, intravenous immunoglobulin, and diazepam have been empirically proposed as treatments of stiff man syndrome.[2 5 6] PEMRS could be responsive to plasmapheresis and immunosupression,[7] but to our knowledge, this is the first case of PEMRS reported in which intravenous immunoglobulin has been successfully used. It seems possible that the successful outcome should be due to the association of prednisone with intravenous immunoglobulin.

The initial clinical picture of this case resembled closely the stiff person syndrome, even with a positive determination of anti-GAD autoantibodies in CSF. PEMRS features appeared some days later. The patient was treated with diazepam, gabapentin, and valproate without any response; moreover, she developed severe muscle spasms and a confusional state. Five days after starting treatment with intravenous immunoglobulin and steroids, the patient reached a normal level of consciousness and the leg cramps disappeared, although she had a moderate loss of strength in her hands and a mild memory loss. When she was discharged 4 weeks later on prednisone (80 mg/day) these were her only symptoms. However, when prednisone was decreased some cramps reappeared and prednisone had to be increased again to the previous dose and an immunoglobulin cycle was needed, obtaining a positive response. She has been free of cramps since then.

We think that intravenous immunoglobulin associated with prednisone could be a useful and life saving treatment for patients with PEMRS.

We thank Dr F Graus (Hospital Clinic i Provincial, Barcelona) for the determination of GAD antibodies.

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CORRESPONDENCE

Benign multiple sclerosis? Clinical course, long term follow up, and assessment of prognostic factors

The study by Hawkins and McDonnell[1] found that in multiple sclerosis, women were more likely than men to have a benign course and that young subjects had a more benign course than older subjects with multiple sclerosis. These findings prompt the question: Do postmenopausal women with multiple sclerosis on estrogen replacement therapy do better than those not taking such therapy? Axonal damage is now recognised to be an important determinant of disability in multiple sclerosis (reviewed in Scolding and Franklin[2] and de Stefano *et al*[3]) and myself and colleagues have recently reported more severe axon loss in crossed corticospinal tracts in the spinal cord in men than women who died with a diagnosis of multiple sclerosis.[4] Estrogen has growth promoting effects on some neurons[5] and thus may have the capacity to protect axons from damage in multiple sclerosis. It might be predicted that estrogen replacement therapy could have a beneficial effect on postmenopausal women with multiple sclerosis.

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The authors reply:

We appreciate the observations of Esiri on our paper. The reasons for the more benign course experienced by both younger and female patients are unclear but the hormonal theory she outlines is interesting and certainly has merit.

It has previously been demonstrated that in experimental allergic encephalomyelitis the animal model of multiple sclerosis, estrogen therapy significantly reduces the severity of the disease compared with placebo treatment and it has further been postulated that this favourable response may be mediated by increased production of Th2 cytokines such as interleukin-10.[1] More pertinent has been the findings on the effect of pregnancy on multiple sclerosis where relapse rate declines antenatally only to increase again during the first 3 months postpartum.[2] Interestingly, relapse rates are at their lowest during the last trimester of pregnancy when estrogen levels are reaching their peak.

The hormonal theory and variation in estrogen levels with age might also help to explain the significant proportion of patients in our study who, after an initially benign course, subsequently slip into the secondary progressive phase and seem to deteriorate at a rate similar to those in the "non-benign" category. Unfortunately we are not placed to confirm whether early menopause is associated with a poorer prognosis or if those taking estrogen replacement therapy enjoy a better prognosis and this is clearly worthy of further study.

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Predicting survival using simple clinical variables: a case study in traumatic brain injury

Signorini *et al*[1] developed a prognostic model to predict survival at 1 year for patients with traumatic brain injury. A strong point is that this model uses variables which are easy and cheap to measure. A thorough statistical analysis was performed, including tests for goodness of fit and checks for influential observations. The model was also validated externally in a more recent group of patients. However, during the external validation the Hosmer-Lemeshow statistic showed a significant lack of calibration ($p<0.0001$).

This implies that the model does not give accurate predictions of the survival of "new" patients. The lack of calibration is especially due to an overly pessimistic prediction in the patients with a poor prognosis but also to a too optimistic prediction for patients with a better prognosis (fig 2).[1] This is typical for "overfitting"—that is, that a model tends to predict too extreme probabilities in new patients.

Overfitting can be limited by several procedures. One of them is that, as a rough estimate, no more than $m/10$ predictor degrees of freedom (df) should be analysed to construct a multiple regression model, where m is the number of events (for example, deaths).[2] As 87 patients died within 1 year, 87/10=8.7 df could be examined during the course of analysis without risk of overfitting. In the paper 6 df were used by the final multivariate prognostic model. However, age was fitted as a piecewise linear variable after using a generalised additive model, requiring an unknown number of df, but always more than one. Furthermore, we assume that easy to achieve variables such as sex (1 df) and cause of injury (3 df) were considered but dropped during model construction. Also some of the candidate variables originate from combined variables when, after initial assessment, it seemed that some categories could be collapsed. Altogether this means that probably much more than 8.7 df were examined.